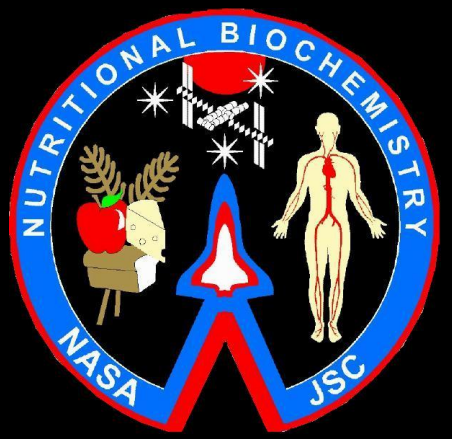
NASA HRP Investigators Symposium 2012

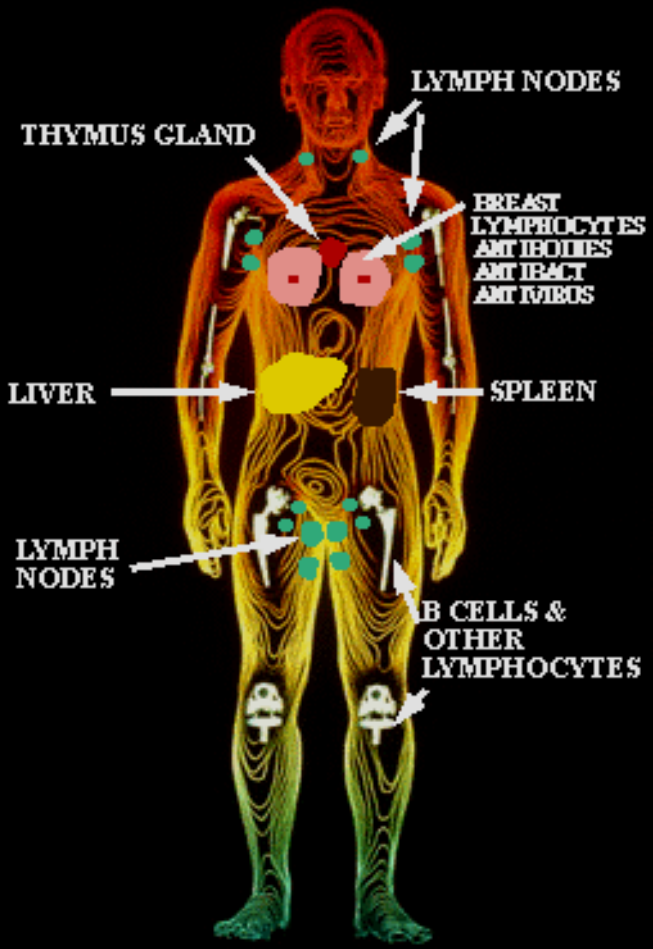
PLASMA CYTOKINE LEVELS DURING LONG-DURATION SPACEFLIGHT

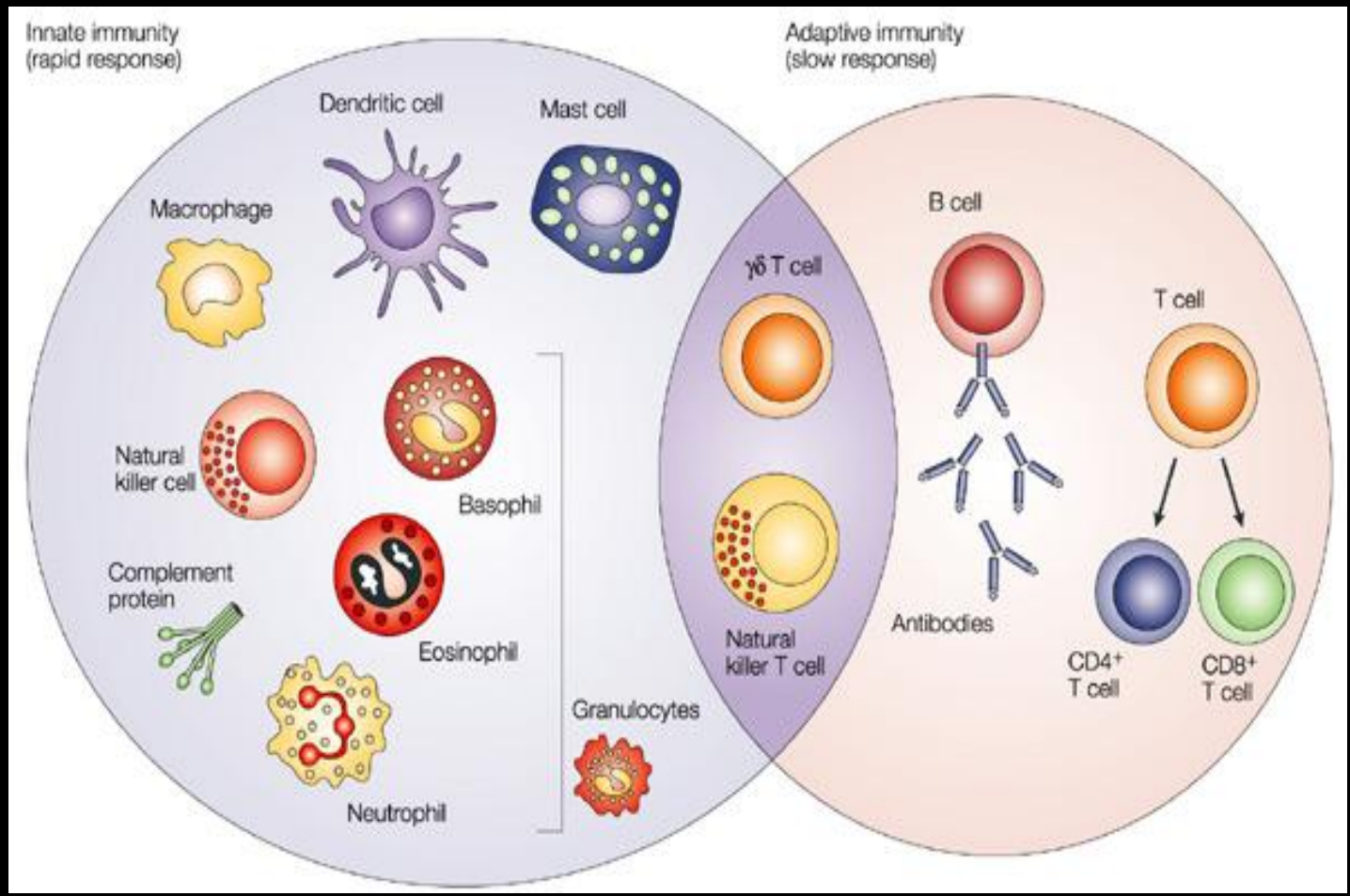
Brian E. Crucian[1], Sara R. Zwart[2], Heather A. Quiriarte[3], Scott M. Smith[1], Clarence F. Sams[1]

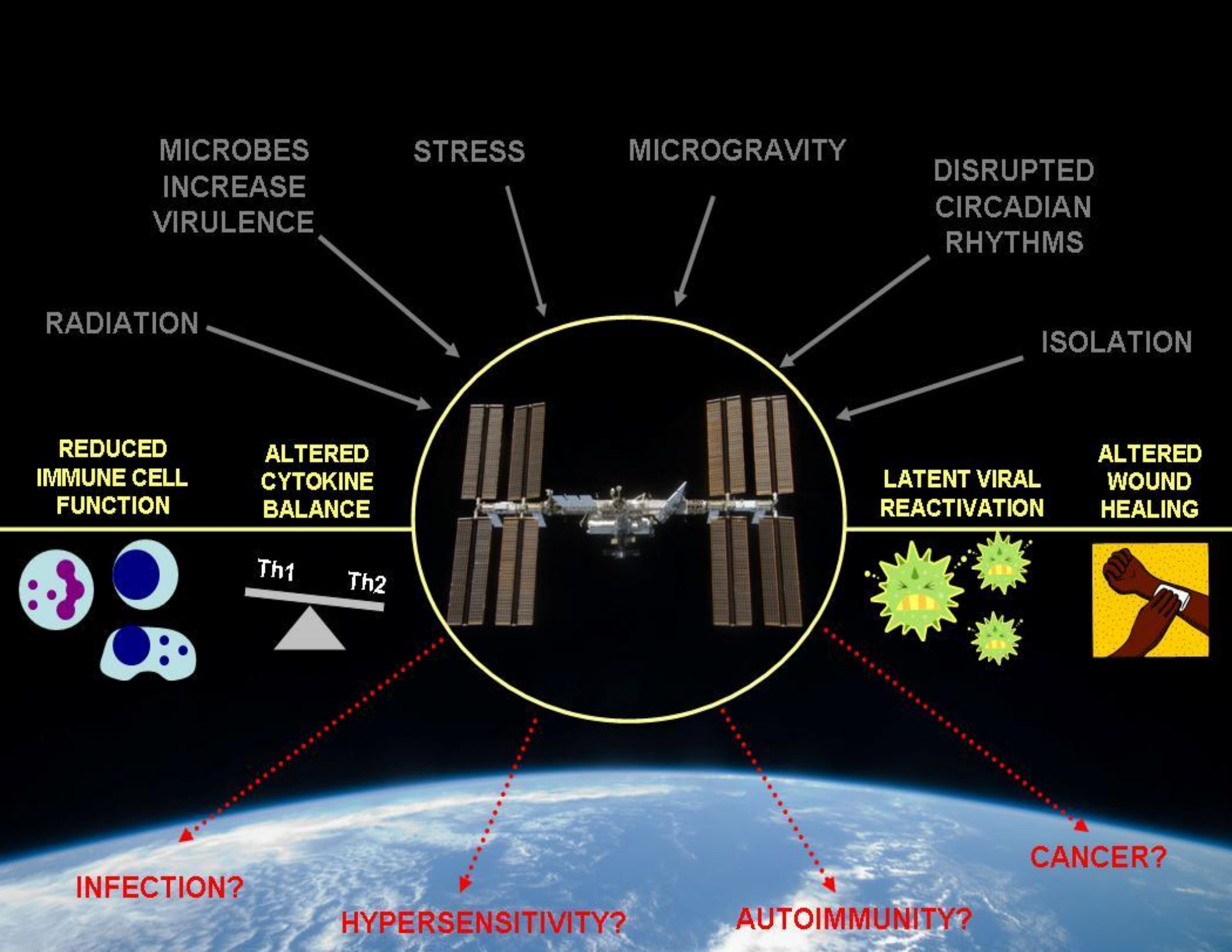
[1]NASA-Johnson Space Center, Houston, Texas, [2]Universities Space Research Association, Houston, Texas, [3]JES Tech, Houston, Texas



THE IMMUNE SYSTEM






MICROBES INCREASE VIRULENCE
STRESS
MICROGRAVITY
DISRUPTED CIRCADIAN RHYTHMS
RADIATION
ISOLATION
REDUCED IMMUNE CELL FUNCTION
ALTERED CYTOKINE BALANCE
Th1
Th2
LATENT VIRAL REACTIVATION
ALTERED WOUND HEALING
INFECTION?
HYPERSENSITIVITY?
AUTOIMMUNITY?
CANCER?

JLB

Review

Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond Earth's orbit?

Nathan Guéguinou,,† Cécile Huin-Schohn,*,† Maithieu Bascove,* Jean-Luc Bueb,† Eric Tschirhart,† Christine Legrand-Frossi,* and Jean-Pol Frippiat*,1*

*Nancy-University, Development and Immunogenetics Team, Vandœuvre-lès-Nancy JE 2537, France; and †University of Luxembourg, Life Sciences Research Unit, Luxembourg

RECEIVED JUNE 11, 2009; ACCEPTED JULY 11, 2009. DOI: 10.1189/jlb.0309167

ABSTRACT

This year, we celebrate the 40th birthday of the first landing of humans on the moon. By 2020, astronauts should return to the lunar surface and establish an outpost there that will provide a technical basis for future manned missions to Mars. This paper summarizes major constraints associated with a trip to Mars, presents immunological hazards associated with this type of mission, and shows that our current understanding of the immunosuppressive effects of spaceflight is limited. Weakening of the immune system associated with spaceflight is therefore an area that should be considered more thoroughly before we undertake prolonged space voyages. *J. Leukoc. Biol.* 86: 1027–1038; 2009.

Introduction

In 1961, Yuri Gagarin became the first human to leave the confines of Earth. Since then, over 450 people have traveled into space, but so far, only 24 astronauts (those of the Apollo missions) have traveled beyond the first 400–500 km of the low-Earth orbit, in which the magnetic field of the Earth deflects a significant fraction of radiation. Beyond the Van Allen radiation belt, where charged particles are trapped in the magnetic field of the Earth, astronauts are exposed to solar and cosmic radiation.

On July 20, 1969, Neil Armstrong and Edwin Aldrin became the first humans to land on the moon. This summer, we celebrated the 40th birthday of this historic event. A few years ago, President George W. Bush proposed a manned return to the moon, with the moon to become the staging post for manned missions to Mars [1]. President Barack H. Obama's 2010 budget request, released on February 26, 2009, confirmed that NASA will stay on track to return to the moon by 2020. A mission to Mars and back will take a minimum of 520 days, of which roughly 1 month will be spent on the martian surface, and the rest will be spent in transit. At its furthest, the crew will be some 360 million km away from home. Consequently, astronauts will have to exercise an unprecedented level of autonomy and teamwork [2]. During the mission, they will experience not only microgravity but also various forms of stress, such as confinement, high expectations of performance, and risks of equipment failure or fatal mishaps. The enormous distance and long travel time to Mars will also probably affect the astronauts psychologically. The crew will therefore endure increased stress levels, radiation, as neither the moon nor Mars has magnetic fields or dense atmospheres that could attenuate them, and microgravity-induced changes, such as alterations in body fluid distribution, which could influence their immune system. As gravity has shaped the architecture of all biological systems on our planet, it is reasonable to observe aberrations in normal functioning of life in weightlessness. A long-term spaceflight will also pose a multitude of health risks, not only those associated with spaceflight, such as bone demineralization, skeletal muscle atrophy, and immune system suppression (**Fig. 1**), but also from common diseases that might cause specific problems under these circumstances. Another risk may be the development of pathogens in a closed environment, where air, food, waste, and water are recycled. Confinement of the crew during flight can and has resulted in the transfer of microorganisms among crew members [4, 5]. Finally, specific health risks might also be encountered on the lunar or martian surface, such as dust or chemicals that could irritate the respiratory tract, for example, or even new organisms. Indeed, 3 days on the moon during the final Apollo mission in 1972 left astronaut Eugene Cernan weary and filthy with rock dust. A trip to Mars will certainly multiply the hazards of space travel.

Humans are ready to accept great risks to go where no one has gone before, but do we have sufficient and sound biologi-

Abbreviations: AHCC=active hexose correlated compound, CNES=French National Space Center, ESA=European Space Agency, Ets=E26 transformation specific, HDBR=head-down bed-rest, IML-2=International Microgravity Laboratory 2, ISS=International Space Station, PKA/PKC=protein kinase A/C, respectively, PMN=polymorphonuclear neutrophil, ROS=reactive oxygen species, SLS-1=Spacelab Life Sciences 1

1. Correspondence: Development and Immunogenetics Team, JE 2537, 9 Avenue de la Forêt de Haye, Faculté de Médecine, 5400 Vandœuvre-lès-Nancy, France. E-mail: jean-pol.frippiat@scbiol.uhp-nancy.fr

J Leukoc Biol 2009;86(5):1027-38

Human Research Program
Human Health Countermeasures Element

Evidence Book

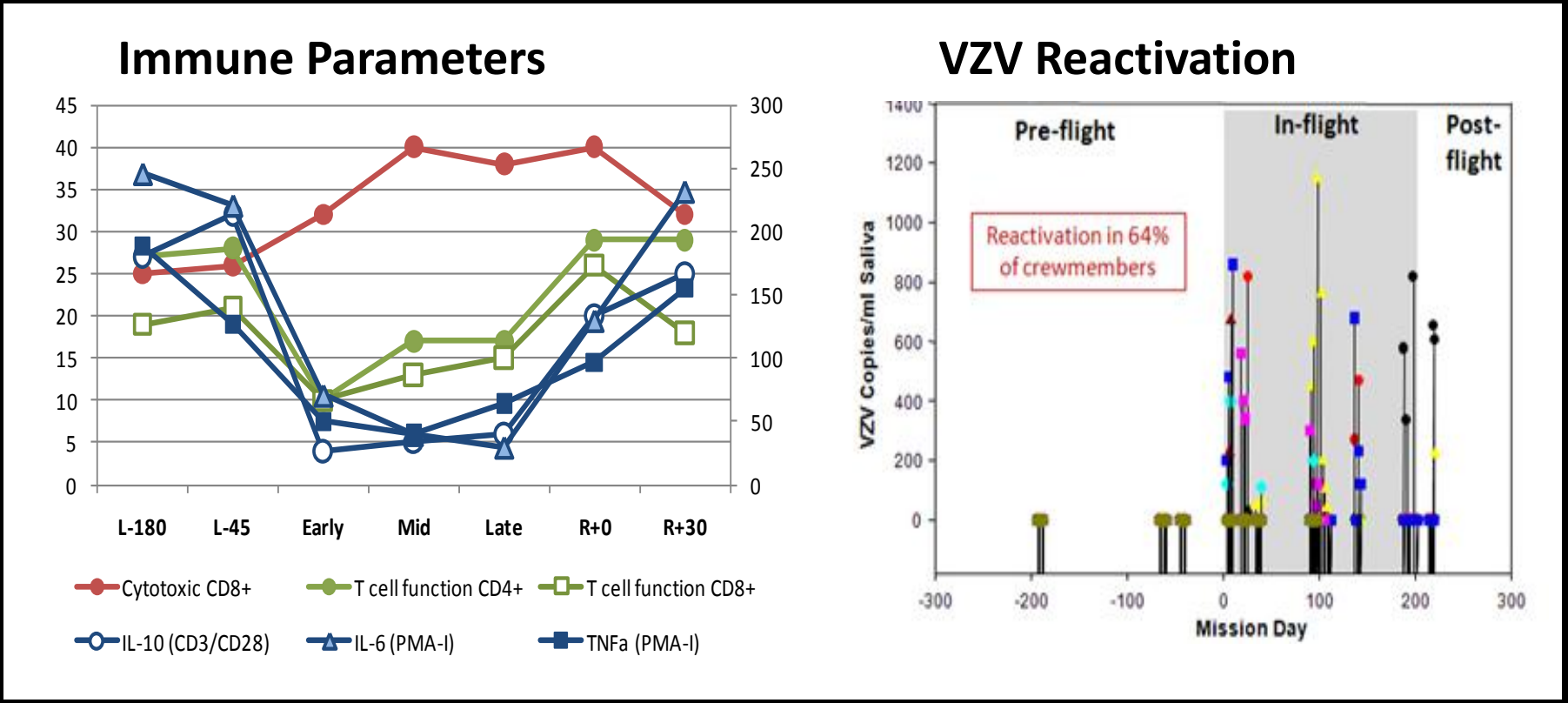
Risk of Crew Adverse Health Event Due to Altered Immune Response

June 2009

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

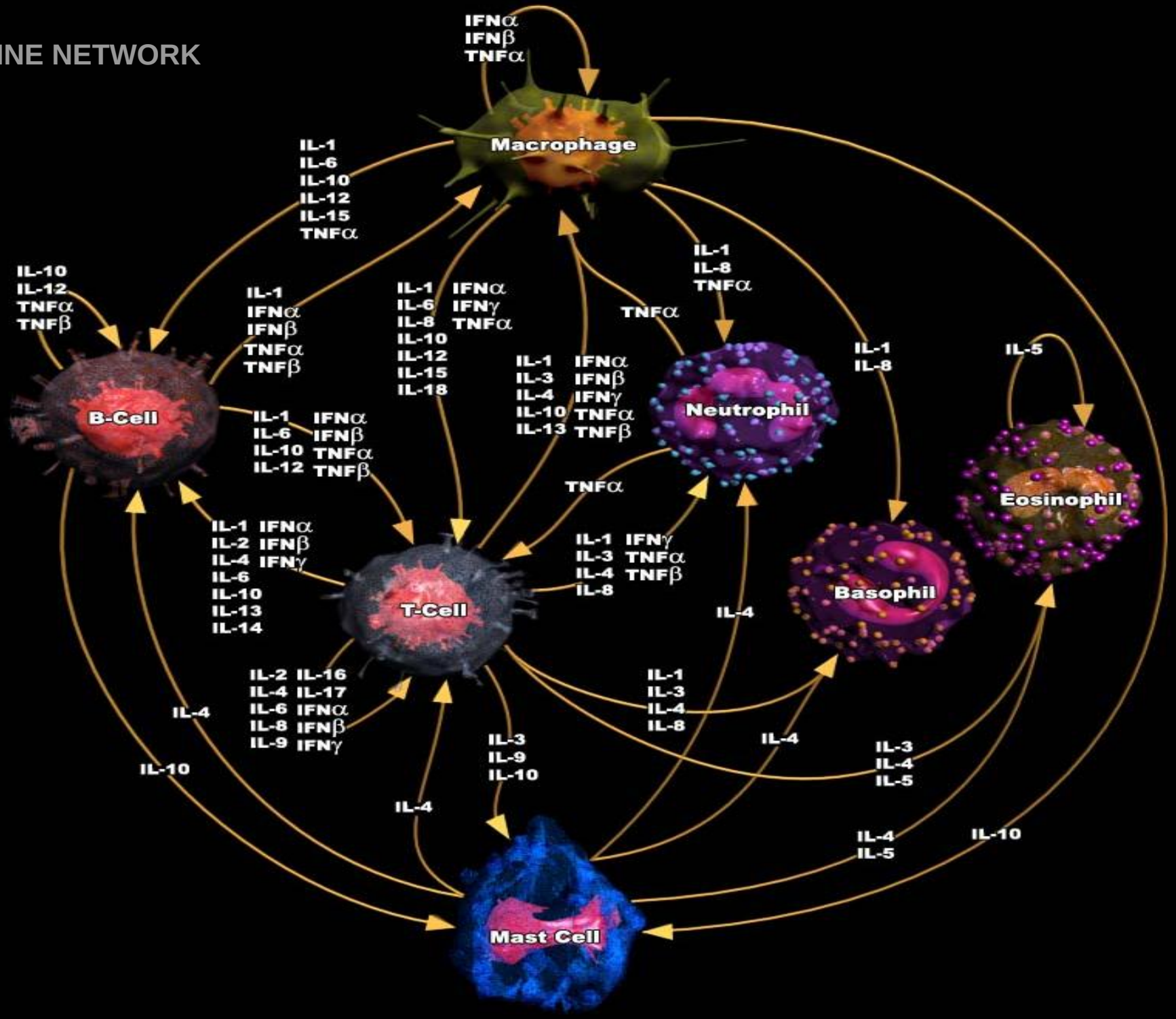
http://humanresearch.jsc.nasa.gov/elements/smo/hrp_evidence_book.asp

Integrated Immune mid-study long duration data (n=10)



Immune dysregulation during deep space missions has the capacity to synergize with other variables such as oxidative damage or radiation exposure. This would further enhance clinical risk to crewmembers.

CYTOKINE NETWORK



Cytokines: Th1/Th2

Th1 - Immunity to intracellular pathogens, viruses

Normal Function

- Cell Mediated 'Inflammatory' Response
- Fight intracellular pathogens (viruses)
- Control DTH response to skin viral/bacterial antigens
- Fight tumor formation
- Phagocyte dependent inflammation

Disease correlations:

Rheumatoid arthritis
organ specific immune disorders
Chohn's disease
Sarcoidosis
Acute allograft rejection
Unexplained recurrent abortions
Multiple sclerosis

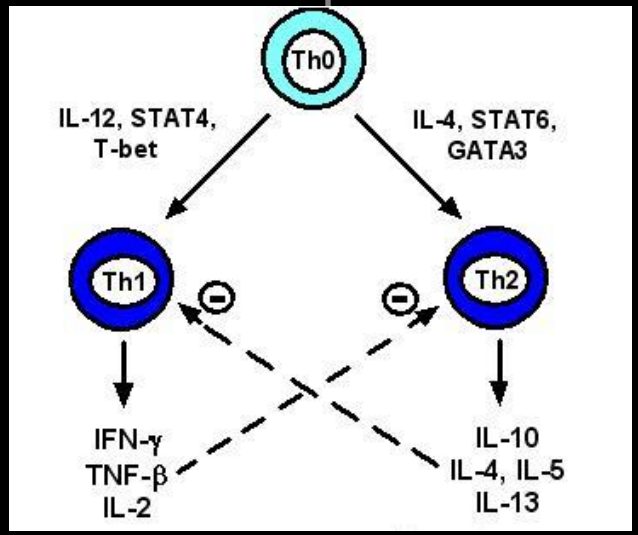
Th2 - Antibody response to extracellular pathogens, parasites

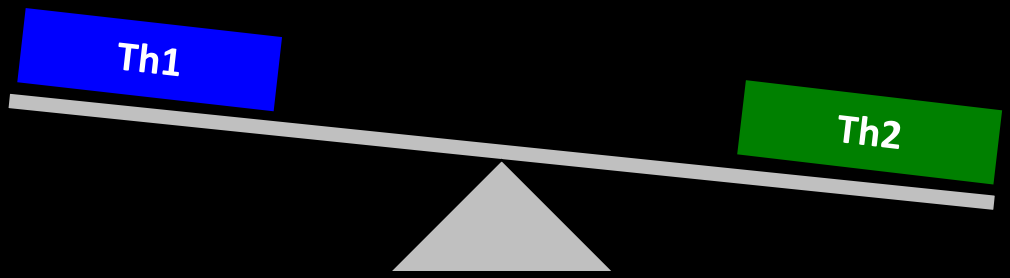
Normal Function

- Humoral (Antibody) Responses
- 'Anti-Inflammatory Response

Disease correlations:

Rapid progression of HIV to AIDS
Chronic graft vs. host disease
Systemic autoimmune diseases
Atopic asthma
Scleroderma
Serum lupus erythematosus
Chronic allergies/sensitization
Atopic dermatitis





Cytokines: Th1/Th2 (updated!)

Naïve CD4+

Environment	Response type	Products	Function
IL-12+IL-18	**Th1** (Monocytic Inf.)	IFNg, IL-2, TNFa, LT	Purpose: CMI, DTH, intracellular pathogens. Pro inflammatory, cause organ secific auto-immunity.
TGFb+IL-6	**Th17** (Neutrophil. Inf.)	IL-17a, f, IL-21, IL-22	Purpose: clear gut bacteria, other pathogens not handled by Th1/2 (citrobacter,k. pheumoniae, candida). Disease: arthritis, MS, psoriasis, EAE.
IL-4+IL-2	**Th2** (Baso/Eo/Mast Inf.)	IL-4, IL-5 (IL-10, 9, 12)	Purpose: humoral immunity, extracellular organisms. Disease: allergy, atopy.
TGFb + IL-4	**Th9**	IL-9, IL-10	IL-9 stimulates proliferation, prevents apoptosis. Effector subset (not regulatory subset). Subset of Th2? Plastic, can switch to Th1 or Th17.
TGFb	**Treg**	TGFb	Natural' Tregs control inflammation, secrete anti-inflammatory cytokines. Reduced Treg function associated with many autoimmune disorders. Express CD25,CD152, icFoxp3.
TGFb+IL-27	**Tr1**	IL-10, TGFb (IL-21 autoc)	Tregulatory type 1 cell: potent immunosuppressive properties, do not express Foxp3. Main tolerance, control autoimmunity, prevent graft rejection, GVH disease
	Th3	TGFb, IL-10	Th3 cells are involved in mucosal immunity. Mediate non inflammatory environment. Promote switch to IgA (non-inflamm, does not activate c', not involved with phagocytosis) Responsible for 'oral tolerance'?
IL-21	**Tfh**	IL-6, IL-10, IL-21	Folicular helper T cells. Regulate step-wise development of ag-specific B cells in vivo. CXCR5+ Deployed to B cell zones of lymphoid tissues

NUTRITION

Proper nutrition is a requirement for a normal immune response. Deficiencies in any of several dietary requirements have been linked to diminished immune function and/or clinical illness

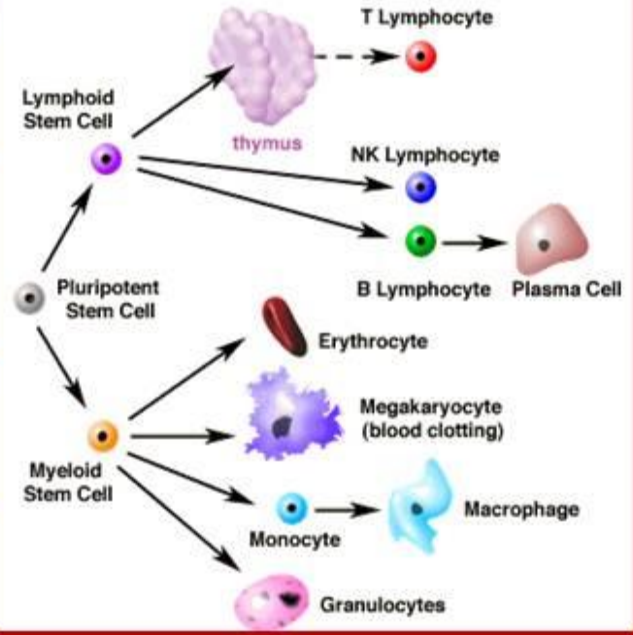
RADIATION

Immune cells generally susceptible to radiation damage. Peripheral T and B cells via apoptosis induction; and via lethal damage to marrow stem cells

BONE

Within the bone marrow cavity, cytokines produced by immune cells also have important effects on regulating bone homeostasis. RANKL, M-CSF, TNF, ILs, and IFNs, affect the differentiation and activity of osteoclasts and bone resorption. During chronic inflammation, the balance of bone modeling and remodeling can be greatly affected.

IMMUNE SYSTEM



NEUROLOGY

A reciprocal flow of information and functional connection exists between the nervous and immune systems. Communication occurs via soluble mediators and cell-cell contacts.

MICROBIOLOGY

Host-pathogen interactions determine susceptibility to disease. Microbial virulence in conjunction with immune status determines the magnitude and outcome of infection

EXERCISE

Research is uncovering a link between moderate, regular exercise and a strong immune system. However, there is also evidence that too much intense exercise can reduce immunity and may even make you sick

Specific Study Objectives

- Determine the in-flight status of immunity, physiological stress, viral immunity/reactivation.
- Specific measurements include leukocyte distribution, T cell function, cytokine production profiles (mRNA, intracellular, secreted, plasma), virus-specific T cell number/function, latent herpesvirus reactivation, stress hormone levels.
- Determine the clinical risk related to immune dysregulation for exploration class spaceflight, as well as an appropriate monitoring strategy for spaceflight-associated immune dysfunction, that could be used for the evaluation of countermeasures.

Determine the nutritional status of astronauts before, during, and after spaceflight ensure adequate intake of energy, protein, and vitamins during missions.

The Clinical Nutritional Status Assessment measures dietary intake, body composition, protein, bone, iron, mineral, vitamin, and antioxidant status (60 total analytes). Currently, it is a medical requirement for U.S. crewmembers on-board the ISS.

The results of data analysis are used both to understand the connections between nutrition and human health during space flight, and to develop effective dietary strategies to reduce adverse health impacts (including bone loss, loss of important vitamins and minerals, and increased genetic damage from radiation).

SAMPLING SCHEDULE

SMO-018

SMO-016

Early
~2 weeks

FD15

FD30

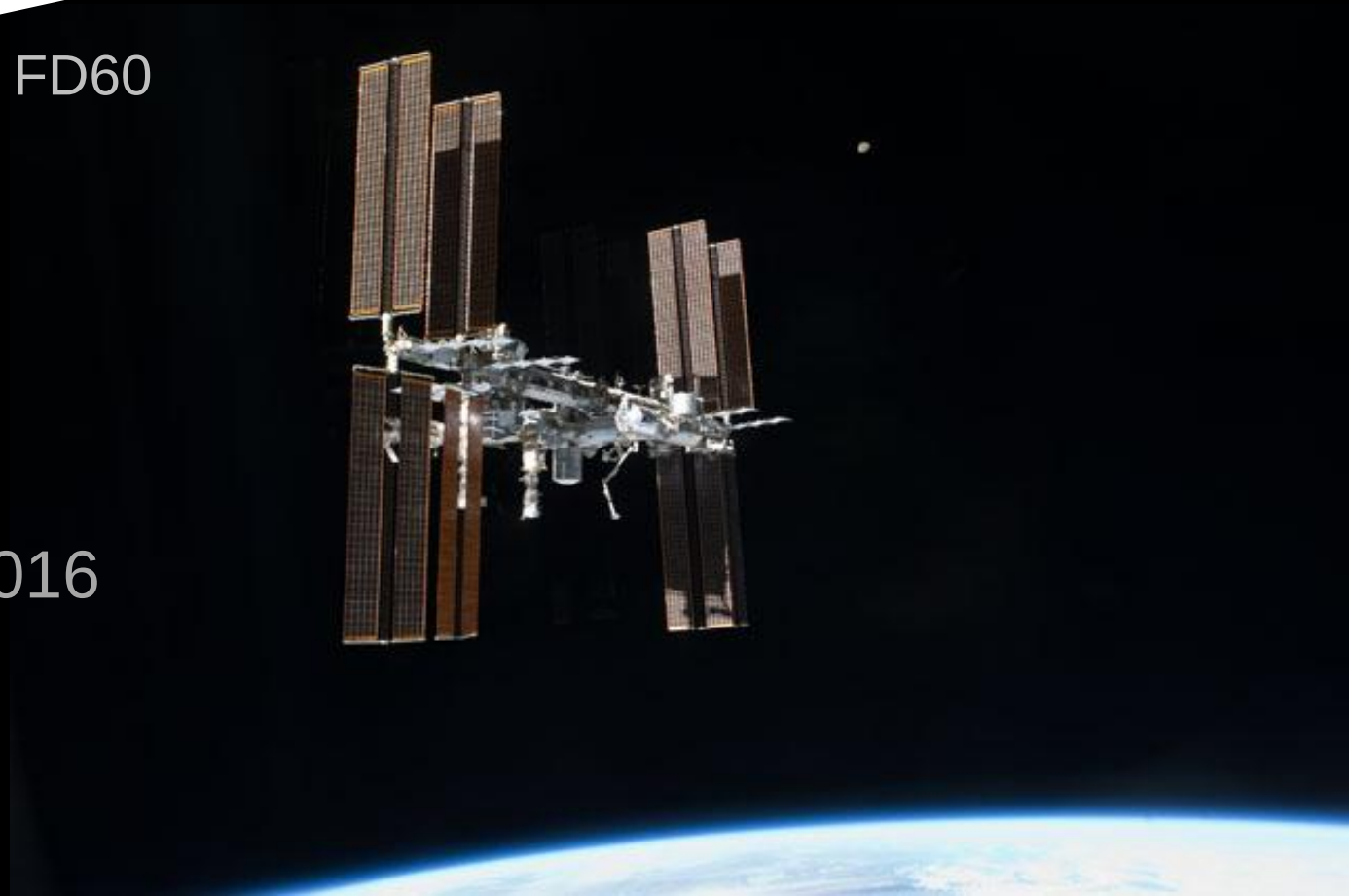
FD60

Mid
2-4 mos

FD120

Late
R-1-2 days

FD180



Cytokine Categories

INFLAMMATORY

IL-1 alpha	
IL-1 beta	
TNF-alpha	+/-
IL-6	

anti-INFLAMMATORY

IL-1ra/IL-1F3	++

GROWTH FACTORS

G-CSF	
GM-CSF	+/-
FGF basic	
Tpo	++
VEGF	

ADAPTIVE/Th1

IFN-gamma	
IL-2	

ADAPTIVE/Th17

IL-17	

ADAPTIVE/Th2

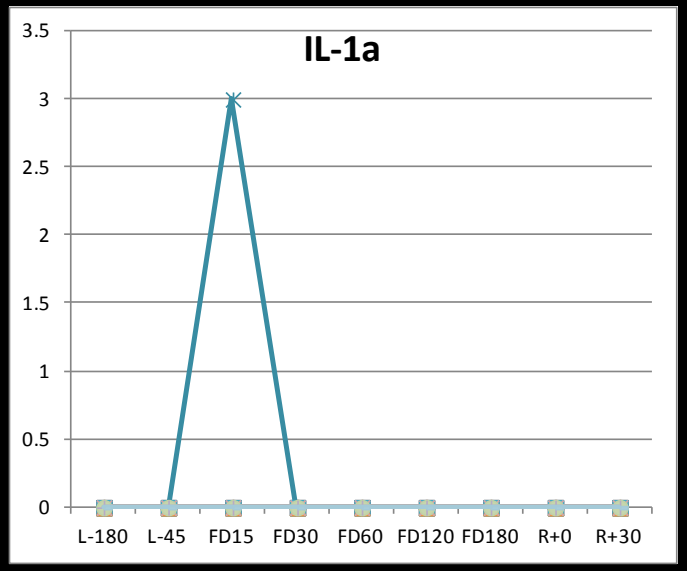
IL-4	
IL-5	
IL-10	

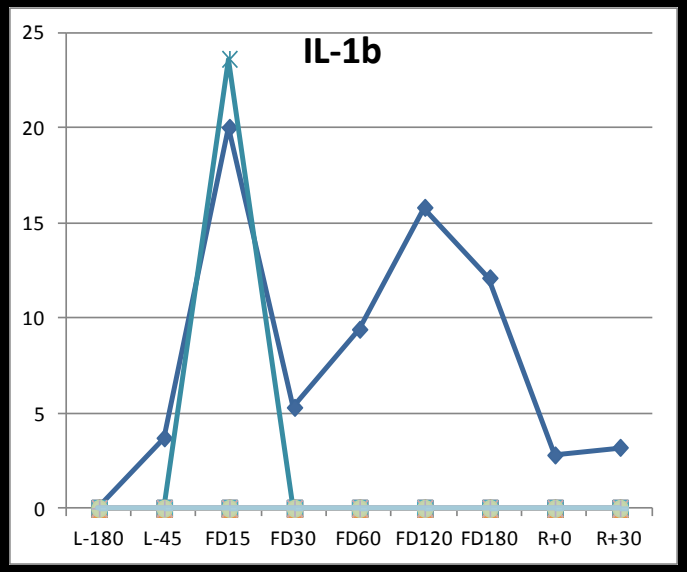
CHEMOKINES

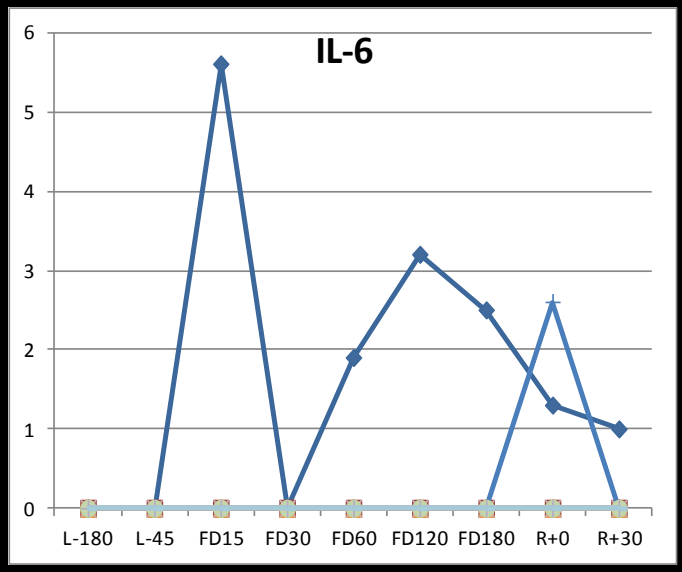
CXCL8/IL-8	+/-
CCL2/MCP-1	
CCL3/MIP-1 alpha	
CCL4/MIP-1 beta	+
CCL5/RANTES	+++
CXCL5/ENA-78	+++

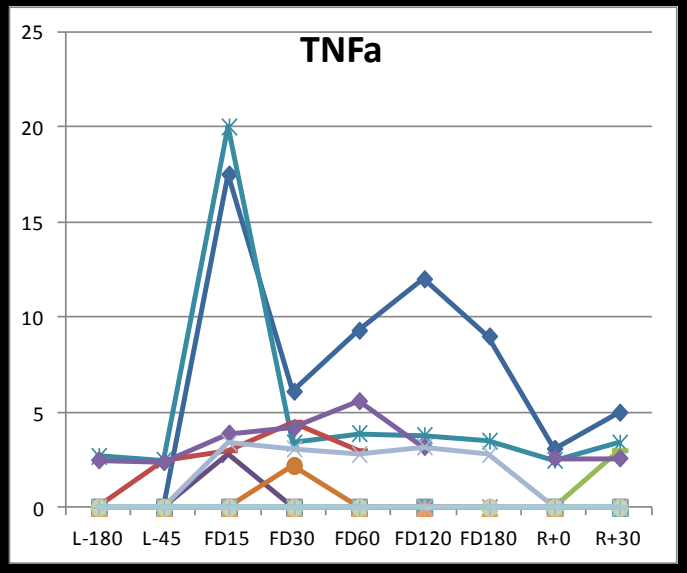
For a 22-cytokine array, assuming a qualitative data, there are 4,194,304 possible outcomes.

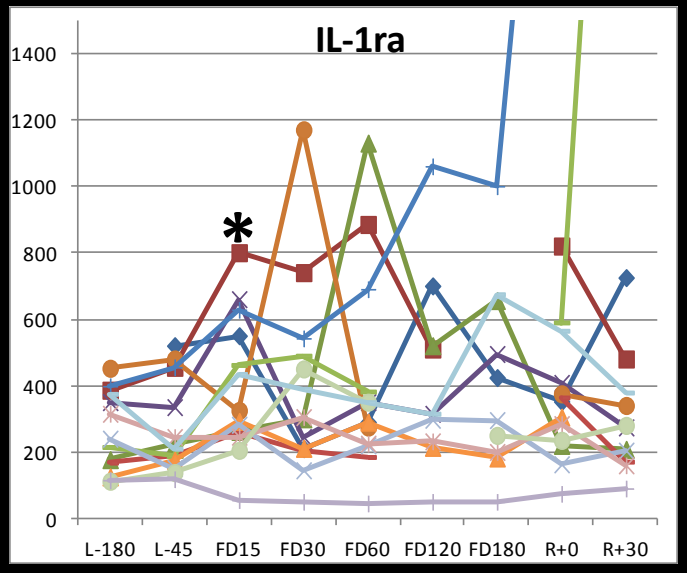
Plasma Cytokine Data – Inflammatory Cytokines



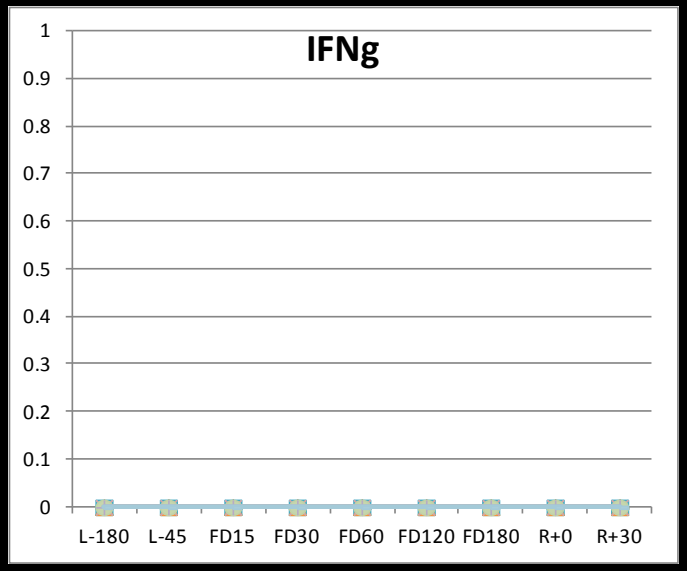


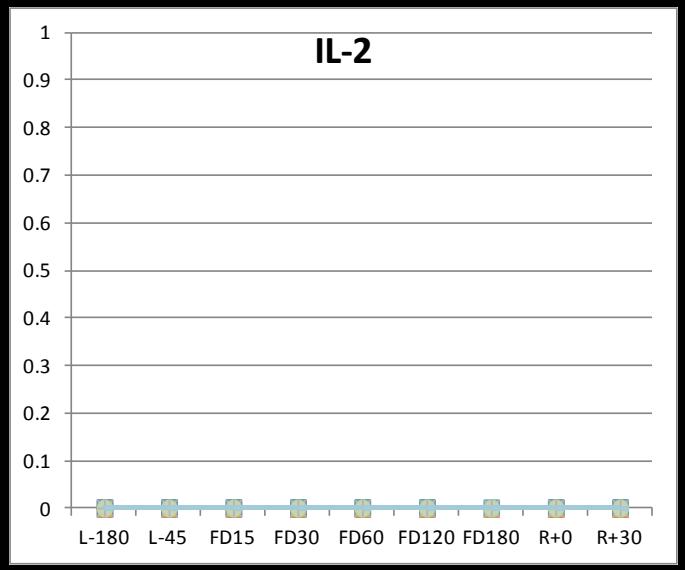


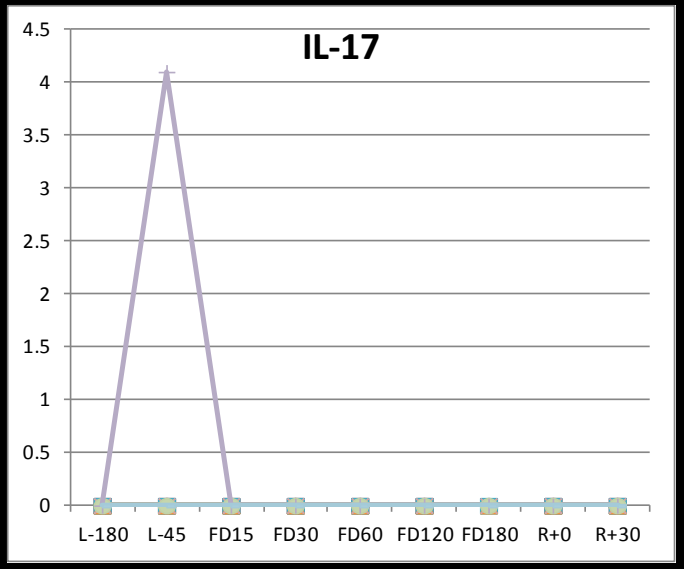


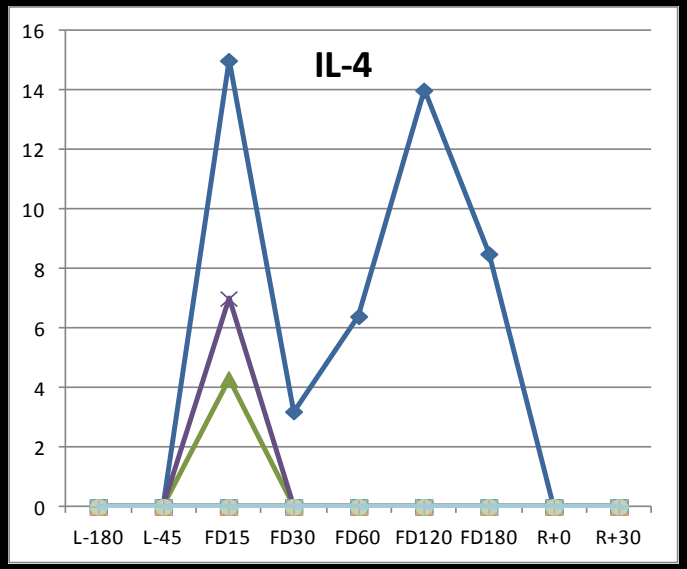


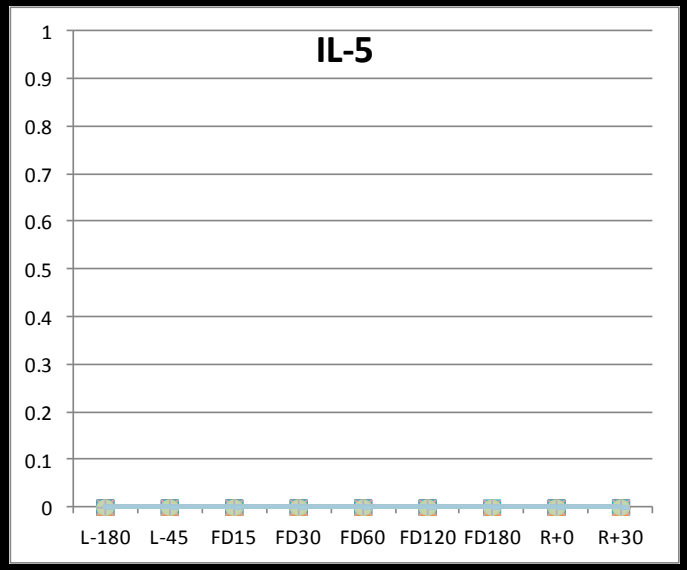
Plasma Cytokine Data – Adaptive Immunity

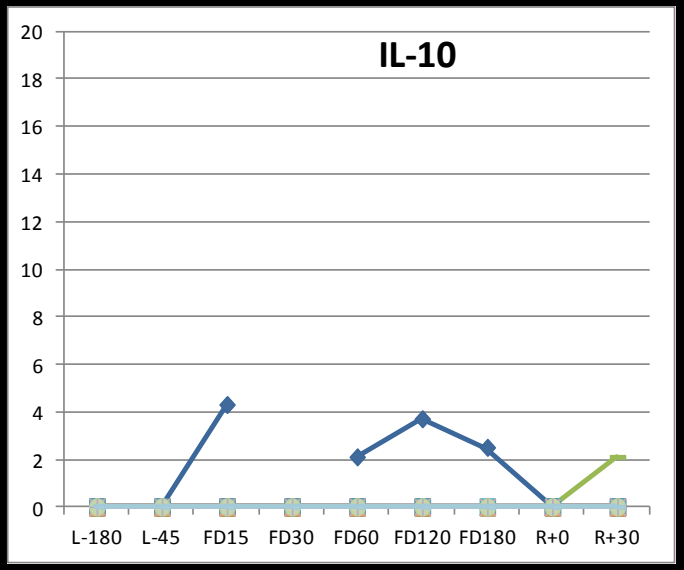




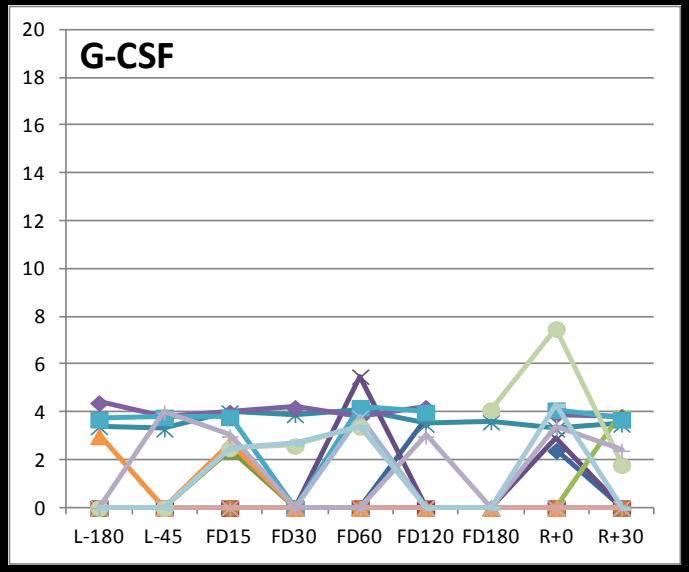


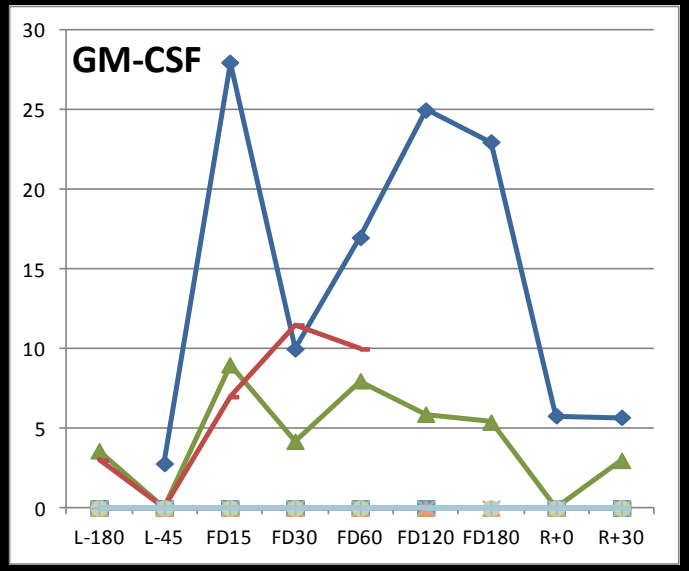


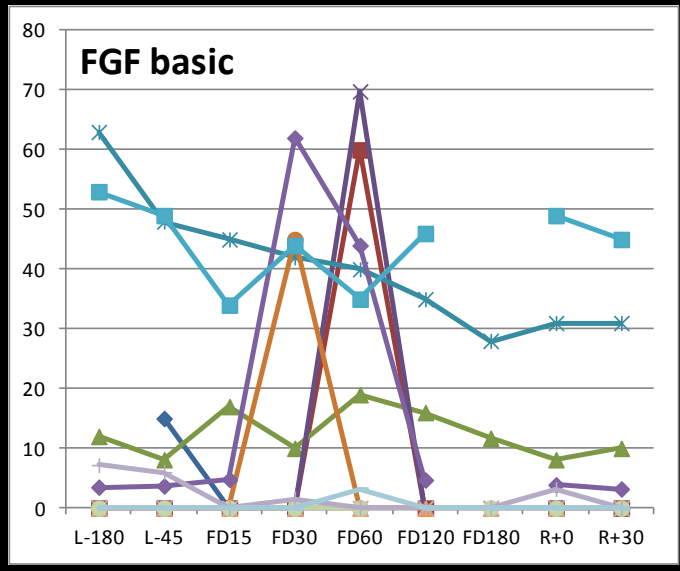


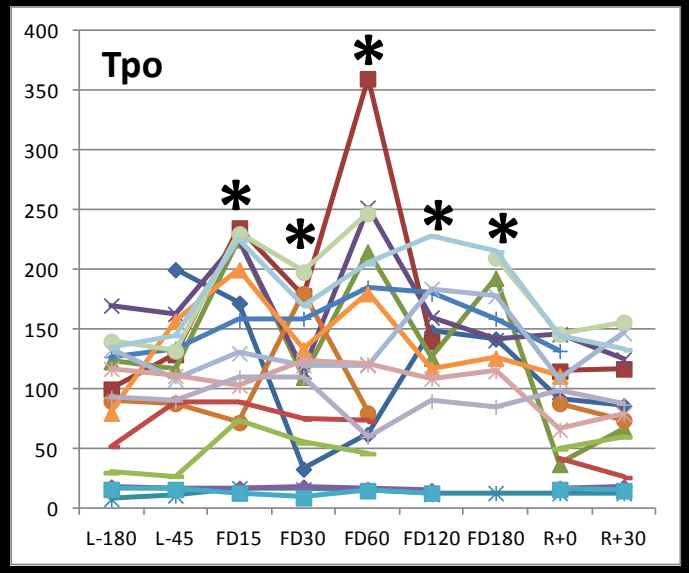


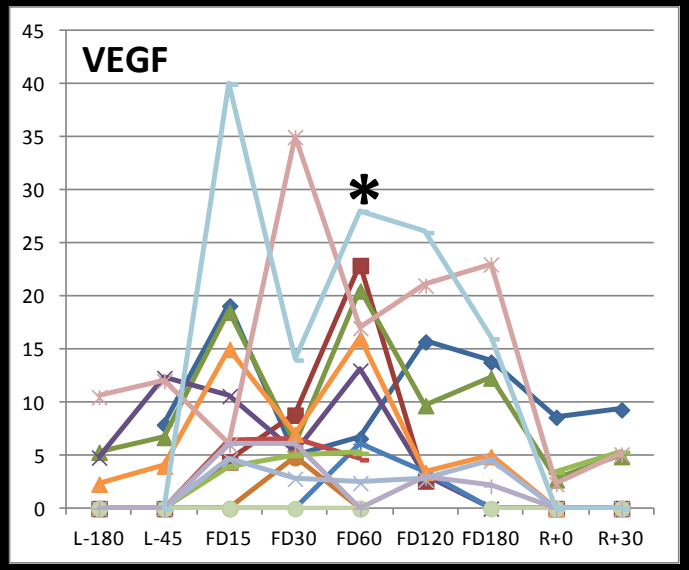
Plasma Cytokine Data – Growth Factors



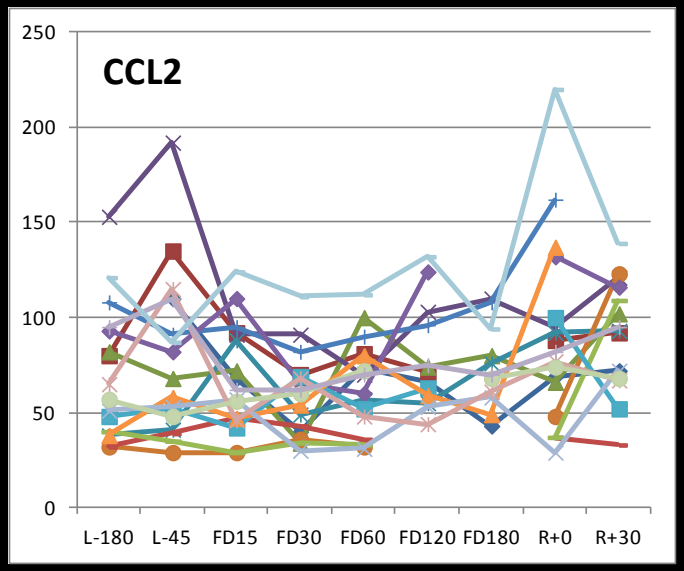


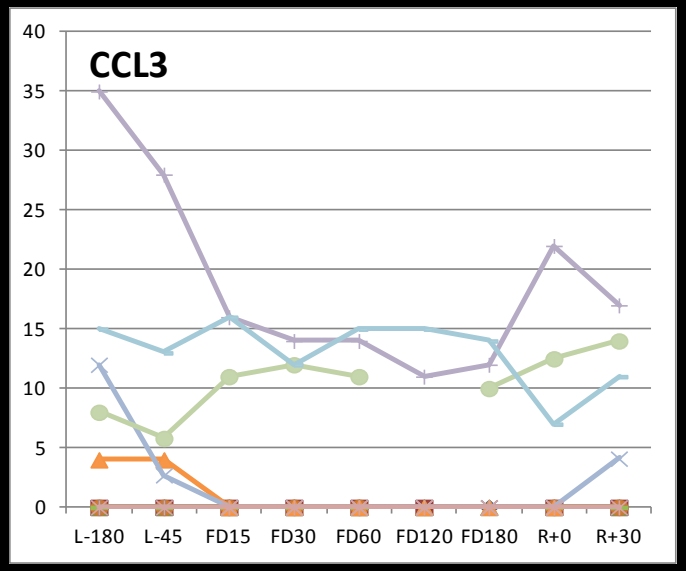


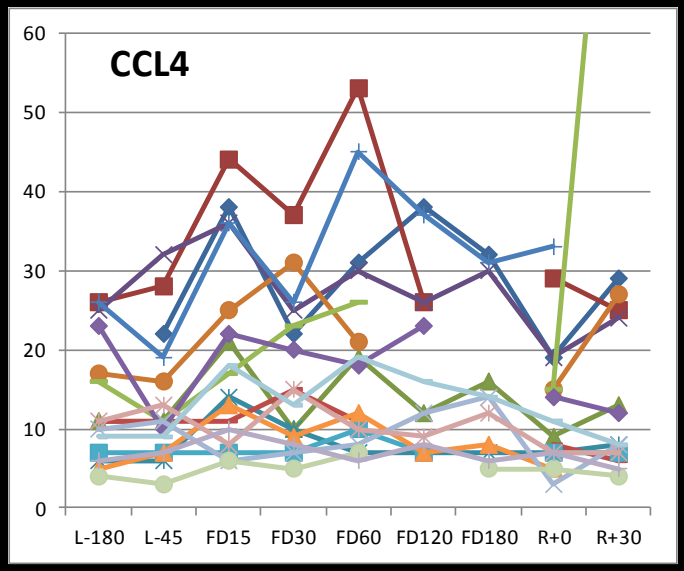


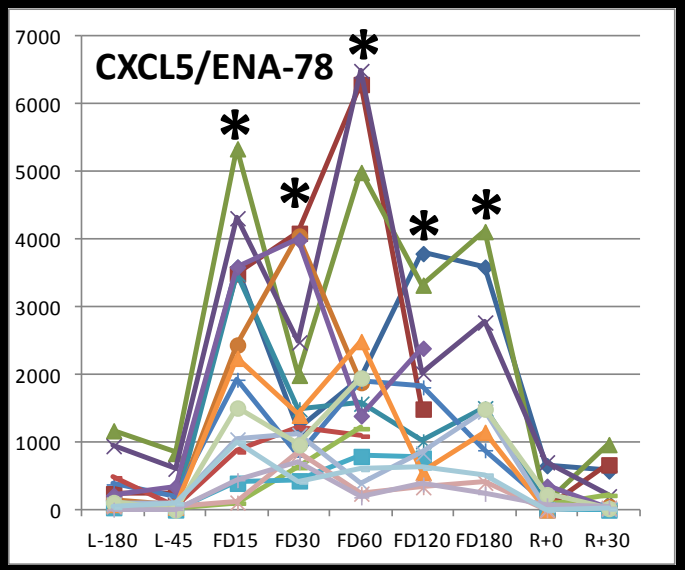


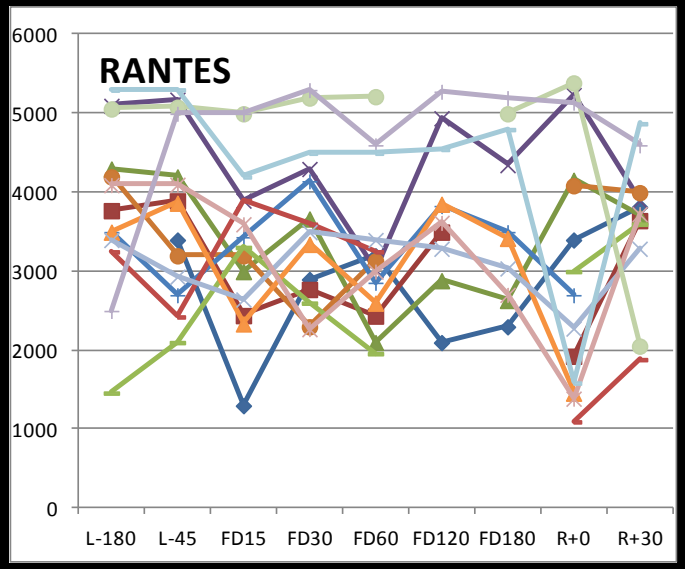
Plasma Cytokine Data – Chemokines

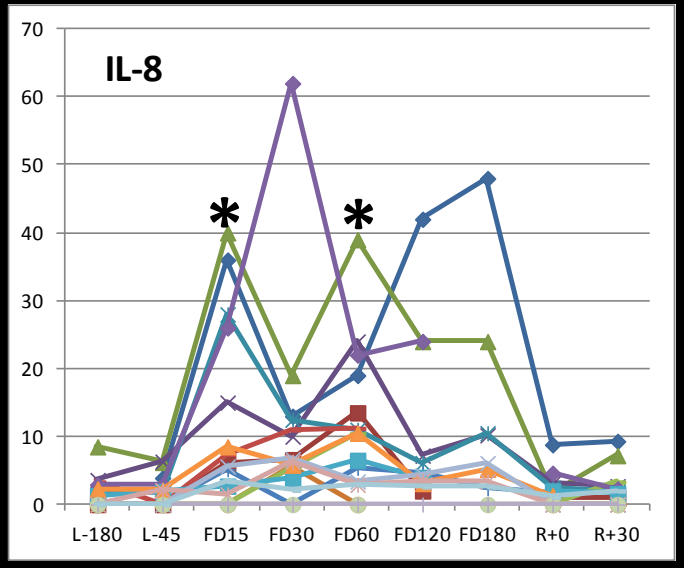












Conclusions

•In general, levels of inflammatory and adaptive immunity cytokines are not elevated during long-duration spaceflight.

•Reduced T cell, granulocyte, NK and monocyte function have all been reported following both long and short duration spaceflight, however no systemic inflammatory or adaptive immune activation evident during spaceflight.

•Increases in growth factors and chemokines may indicate other types of adaptation occurring during spaceflight, such as attempts to overcome diminished immunocyte function.

•Are there localized inflammatory processes that result in a downstream peripheral manifestation (IL-1ra, CXCL5, IL-8)?

•There appear to be varied individual crew responses, and specific relationships between cytokines and markers of iron status and muscle turnover that warrant further evaluation.